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INVITED COMMENTARY

Prostate Cancer

Dexamethasone use in metastatic castration-resistant prostate cancer patients treated with abiraterone acetate: this "cort" is not out of order!

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In the recent issue of *Asian Journal of Andrology*, Ni *et al.*[1] explore a therapeutic reflex that we as clinicians have developed over the years when treating patients with metastatic castration-resistant prostate cancer (mCRPC) with abiraterone acetate (AA). With the first signs of progression, usually, this is a rising prostate-specific antigen (PSA) level; we often continue AA but switch corticoid from prednisone to 0.5 mg of dexamethasone daily. In a subset of patients, this causes a temporary PSA decline lasting several months to occasionally over a year. It is a very cheap, well-tolerated, and safe option, although evidence for a long-term oncological benefit, such as an overall survival (OS) increase, is lacking.[1]

The true underlying mechanism of this corticoid switch remains unclear, but there are two possible theories: dexamethasone might counter tumor resistance to AA or dexamethasone might have a direct antitumor effect itself. This latter theory seems to be the more plausible. Historical phase II trials, performed before AA entered clinical practice, demonstrated that dexamethasone monotherapy may induce a PSA response (≥50% decline) in up to 61% of mCRPC patients.[2] One phase II trial randomized 82 chemotherapy-naive mCRPC patients to either 0.5 mg of dexamethasone once daily or 5 mg of prednisone twice daily. PSA response rate was 47% versus 24%, respectively ($P = 0.05$).[3] Interestingly, this 23% difference between both groups is almost equal to the 24.8% of patients who had a PSA response following switch from prednisone to dexamethasone in the study of Ni *et al.*[1] Compared to prednisone, dexamethasone more potently activates the glucocorticoid receptor. It has an antiangiogenic effect through inhibition of interleukin-6 and vascular endothelial growth factor. It also decreases the production of insulin-like growth factor-1, which is known as an antiapoptotic molecule.[4]

Instead of performing a corticoid switch, would it not be better to start patients with AA+dexamethasone in the first place? There is some evidence to support this. Attard *et al.*[5] performed a randomized phase II safety study on mCRPC with AA and four different glucocorticoid regimens: prednisone 5 mg twice or once daily, 2.5 mg twice daily, or dexamethasone 0.5 mg once daily. Prednisone 5 mg twice daily and dexamethasone were the only regimens that showed no increased mineralocorticoid excess. Dexamethasone was associated with a higher PSA response rate (88% *vs* 60%–78%) and longer radiographic progression-free survival (26.6 months *vs* 12.8–18.5 months), although the study was not powered to demonstrate oncological superiority. However, compared to prednisone, dexamethasone was associated with increased insulin resistance and decreased bone mineral density.[5]

Which patients under AA+prednisone are the best candidates for a switch to dexamethasone? The proposed models by Ni *et al.*[1] estimate biochemical relapse-free survival (based on serum alkaline phosphatase [ALP] and AKR1C3 expression) and OS (based on serum ALP and PSA). These are, however, not predictive but prognostic models. They can be informative for clinicians and patients to estimate survival but are not predictive for PSA response following corticoid switch. However, previous observational studies (summarized in Supplementary Table 1 by Ni *et al.*[1]) and common sense give us some indications. Metastatic prostate cancer patients who responded to AA+prednisone and experienced biochemical progression in the absence of gross radiographical and clinical progression tend to be ideal candidates for corticoid switching. On the other hand, for heavily pretreated mCRPC patients who did not respond to AA or who have a limited life expectancy, earlier exploration of life-prolonging drugs could be better suited. Finally, a corticoid switch also is a viable option in patients who have no further life-prolonging treatments available.

COMPETING INTERESTS

All authors declare no competing interests.

REFERENCES

1 Ni YC, Zhao JG, Zhang MN, Zhang YJ, Yang ZY, *et al*. Predictors of efficacy of corticosteroid switching from abiraterone plus prednisone to dexamethasone in patients with metastatic castration-resistant prostate cancer. *Asian J Androl* 2021. Doi: 10.4103/aja202143. [Online ahead of print].
2 Storlie JA, Buckner JC, Wiseman GA, Burch PA, Hartmann LC, *et al*. Prostate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma. *Cancer* 1995; 76: 96–100.
3 Venkitaraman R, Lorente D, Murthy V, Thomas K, Parker L, *et al*. A randomised phase 2 trial of dexamethasone versus prednisolone in castration-resistant prostate cancer. *Eur Urol* 2015; 67: 673–9.
4 Kassi E, Moutsatsou P. Glucocorticoid receptor signalling and prostate cancer. *Cancer Lett* 2011; 302: 1–10.
5 Attard G, Merseburger A, Arlt W, Sternberg CN, Feyerabend S, *et al*. Assessment of the safety of glucocorticoid regimens in combination with abiraterone acetate for metastatic castration-resistant prostate cancer: a randomized, open-label phase 2 study. *JAMA Oncol* 2019; 5: 1159–67.

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